

This study was supported by the Institut Hospitalo-Universitaire Méditerranée Infection, the French National Research Agency under the Investissements d'avenir programme, (reference ANR-10-IAHU-03), and the fourth Make Our Planet Great Again (MOPGA 4) program. This work was cofunded by the Labex Dispositif de Recherche Interdisciplinaire sur les Interactions Hommes-Milieus, and the Investissements d'Avenir program (ANR-11-LABX-0010), which is managed by the Agence nationale de la recherche.

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## References

1. Angelakis E, Raoult D. Q fever. *Vet Microbiol*. 2010;140:297–309. <https://doi.org/10.1016/j.vetmic.2009.07.016>
2. Tissot-Dupont H, Raoult D. Q fever. *Infect Dis Clin North Am*. 2008;22:505–14, ix. <https://doi.org/10.1016/j.idc.2008.03.002>
3. Vanderburg S, Rubach MP, Halliday JEB, Cleaveland S, Reddy EA, Crump JA. Epidemiology of *Coxiella burnetii* infection in Africa: a OneHealth systematic review. *PLoS Negl Trop Dis*. 2014;8:e2787. <https://doi.org/10.1371/journal.pntd.0002787>
4. Mediannikov O, Fenollar F, Socolovschi C, Diatta G, Bassene H, Molez J-F, et al. *Coxiella burnetii* in humans and ticks in rural Senegal. *PLoS Negl Trop Dis*. 2010;4:e654. <https://doi.org/10.1371/journal.pntd.0000654>
5. Angelakis E, Mediannikov O, Socolovschi C, Mouffok N, Bassene H, Tall A, et al. *Coxiella burnetii*-positive PCR in febrile patients in rural and urban Africa. *Int J Infect Dis*. 2014;28:107–10. <https://doi.org/10.1016/j.ijid.2014.05.029>
6. Sokhna C, Mediannikov O, Fenollar F, Bassene H, Diatta G, Tall A, et al. Point-of-care laboratory of pathogen diagnosis in rural Senegal. *PLoS Negl Trop Dis*. 2013;7:e1999. <https://doi.org/10.1371/journal.pntd.0001999>
7. Dahmana H, Granjon L, Diagne C, Davoust B, Fenollar F, Mediannikov O. Rodents as hosts of pathogens and related zoonotic disease risk. *Pathogens*. 2020;9:202. <https://doi.org/10.3390/pathogens9030202>
8. Sikes RS, Gannon WL; Animal Care and Use Committee of the American Society of Mammalogists. Guidelines of the American Society of Mammalogists for the use of wild mammals in research. *J Mammal*. 2011;92:235–53. <https://doi.org/10.1644/10-MAMM-F-355.1>
9. Diouf FS, Ndiaye EHI, Hammoud A, Diamanka A, Bassene H, Ndiaye M, et al. Detection of *Coxiella burnetii* and *Borrelia* spp. DNA in cutaneous samples and in household dust in rural areas, Senegal. *Vector Borne Zoonotic Dis*. 2021;21:659–66. <https://doi.org/10.1089/vbz.2020.2723>
10. Granjon L, Ba K, Diagne C, Ndiaye A, Piry S, Thiam M. The Ferlo small rodent community: historical trends and characteristics of the current population [in French]. In: Boëtisch G, Duboz P, Guissé A, Sarr P, editors. *The Great*

Green Wall, an African response to climate change [in French]. Paris: Centre national de la recherche scientifique; 2019. p. 1–19.

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## Therapeutic Failure and Acquired Bedaquiline and Delamanid Resistance in Treatment of Drug-Resistant TB

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DOI: <http://doi.org/10.3201/eid2905.221716>

New classes of antitubercular drugs, diarylquinolines and nitroimidazoles, have been associated with improved outcomes in the treatment of drug-resistant tuberculosis, but that success is threatened by emerging drug resistance. We report a case of bedaquiline and delamanid resistance in a 55-year-old woman in South Africa with extensively drug-resistant tuberculosis and known HIV.

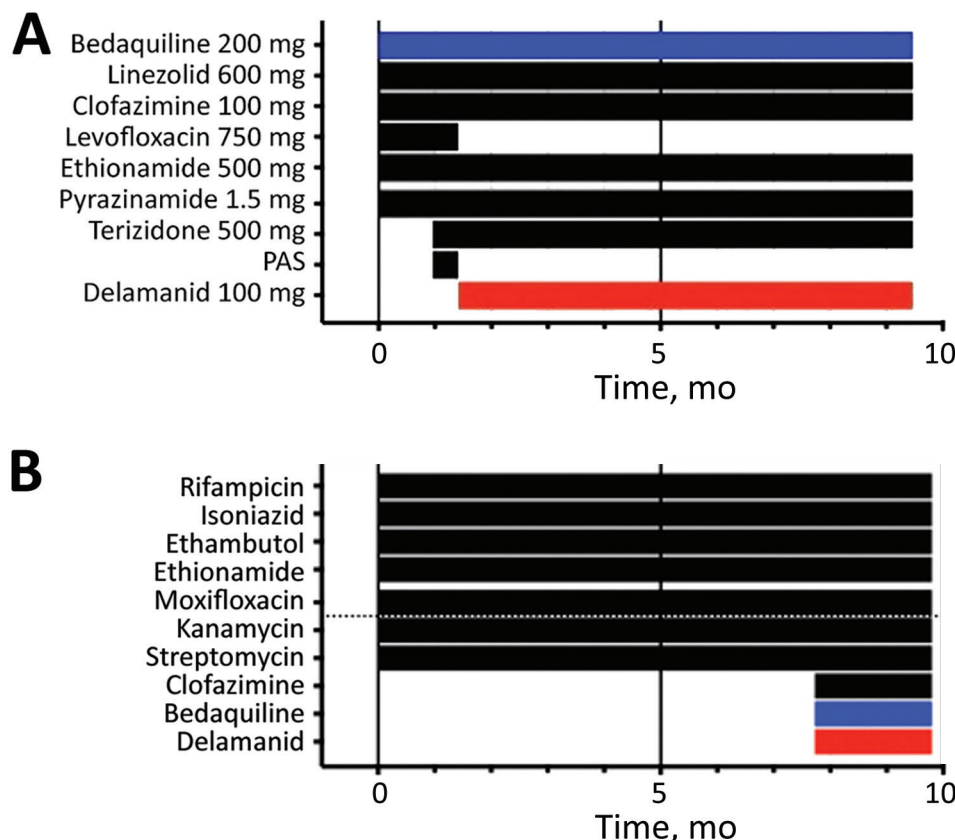
Major improvements have been achieved in drug-resistant tuberculosis (TB) treatment in recent years; 2 new drug classes, diarylquinolines (bedaquiline) and nitroimidazoles (pretomanid and delamanid), have been central to this success (1). The Ze-NiX trial demonstrated cure rates of >90% in complex

drug-resistant TB when a bedaquiline, pretomanid, and linezolid (BPaL) regimen was given for just 6 months (2); the TB-PRACTECAL trial used BPaL plus moxifloxacin to treat multidrug-resistant (MDR) TB and achieved cure rates of 89% versus 50% in controls (3). These regimens have been recommended as the preferred treatment option for drug-resistant TB by the World Health Organization (4).

Threatening those recent successes, resistance can emerge to bedaquiline through mutations in *atpE*, *pepQ*, or *Rv0678* (with mutations in *Rv0678* being by far the most common in clinical isolates) and to pretomanid and delamanid through mutations of *fbtA/B/C*, *ddn*, and *fgd1*. Bedaquiline resistance has been increasingly reported, but only a handful of cases of resistance to both classes of agents in TB patients have been reported (4–8). All of those reports have described prolonged infections treated with differing drug combinations over time, and none were cases where all 3 components of BPaL were administered concurrently. We present the case of a patient with pre-XDR TB (resistant to rifampin, isoniazid, and fluoroquinolones) in South Africa whose treatment regimen failed when bedaquiline resistance and subsequent delamanid resistance developed, despite treatment with bedaquiline, delamanid, and linezolid beginning early in therapy.

A 55-year-old woman sought care in July 2018 for weight loss and fatigue. She had completed treatment for drug-susceptible TB in 2007 and received an HIV diagnosis in 2012 (initial viral load 31,222 copies/mL and CD4 count 174 cells/ $\mu$ L) that was treated with efavirenz/emtricitabine/tenofovir. Chest radiography revealed extensive cavitary pulmonary TB. She had no other medical diagnoses. Initial sputum smear showed 3+ acid-fast bacilli and was culture-positive for *Mycobacterium tuberculosis* consistent with rifampin resistance by the Xpert MTB/RIF assay (Cepheid, <https://www.cephheid.com>).

A 9-month oral regimen consisting of bedaquiline, linezolid, clofazimine, levofloxacin, ethionamide, and pyrazinamide was commenced in line with guidelines in South Africa at the time, and the patient was enrolled in the PRAXIS study, a randomized controlled trial of bedaquiline adherence support (9). Antiretroviral drugs were changed to nevirapine/emtricitabine/tenofovir to manage interactions with bedaquiline. GenoType MTBDRplus and MTBDRsl (Hain Lifescience, <https://www.hain-lifescience.de>) line probe assay results and phenotypic drug susceptibility testing (DST) on the baseline culture confirmed resistance to rifampin, isoniazid, and fluoroquinolones. Because of fluoroquinolone resistance, we changed



**Figure.** Drug regime over time of patient with drug-resistant tuberculosis, South Africa. A) Drug treatment history by month. B) Development of drug resistance according to phenotypic drug susceptibility testing per month. Red indicates delamanid, blue indicates bedaquiline. PAS, P-aminosalicylic acid.

treatment to a modified World Health Organization long regimen (minimum 18 months) and added terizidone and p-aminosalicylic acid. Delamanid became available through an expanded-access program and was added at week 6 when levofloxacin and p-aminosalicylic acid were stopped.

We assessed adherence to bedaquiline and antiretrovirals using a Wisepill medication dispenser (Wisepill Technologies, <https://www.wisepill.com>). We conducted extended-phenotypic DST at weeks 6 and 34 and performed whole-genome sequencing (WGS) at weeks 6, 14, and 34. We assessed MICs for a range of drugs on week 6 isolates and week 34 isolates by using a microtiter plate (9). Phenotypic DST at week 6 demonstrated additional resistance to moxifloxacin, ethionamide, ethambutol, streptomycin, and kanamycin; we observed corresponding mutations in *rpoB*, *katG*, *gyrA*, *ethA*, *embB*, and *rrs* (Figure; Appendix Figure, <https://wwwnc.cdc.gov/EID/article/29/5/22-1716-App1.pdf>). At week 10, the patient was discharged from hospital for outpatient management.

Despite therapy, she remained smear-positive and culture-positive at week 34 and had lost a further 5 kg. We extended bedaquiline to 9 months. Bedaquiline adherence from initiation of therapy was 45%. WGS at week 14 identified acquisition of 2 bedaquiline resistance-associated variants (RAVs) in *Rv0678*: one was a single-nucleotide variation (Gln22Pro) and the other was an insertion (Asp47frameshift). WGS at week 34 demonstrated acquisition of a further 6 *Rv0678* bedaquiline RAVs (Ala57Glu, Arg72Trp, Asp88frameshift, Asp88Ala, Gly121Arg, Leu122Pro) and the emergence of 2 heterozygous *fbiC* loss-of-function mutations (Ala487frameshift, 25%; Ser534stop, 12%). Phenotypic DST at week 34 confirmed emergent resistance to bedaquiline and clofazimine, which commonly demonstrates cross-resistance with bedaquiline because of *Rv0678* mutations (Figure). Delamanid phenotypic DST by microtiter plate confirmed an increase in delamanid MIC from 0.015 to >0.5 µg/mL, consistent with resistance (10). The patient died ≈10 months after initial diagnosis and treatment initiation.

Recent clinical trial evidence from ZeNix-TB and TB-PRACTECAL has been extremely encouraging for the development of an effective, 6-month regimen for complex drug-resistant TB (2,3). Despite promising clinical trial results, this case highlights the ease with which resistance can develop in real-world implementation, likely because of the complex interplay of factors such as inadequate regimens caused by delayed or limited DST, drug pharmacokinetics, lesion penetration of drugs, and medication adherence. As regimens based on BPAL are rolled out more widely,

combining this treatment with contemporaneous access to rapid DST for all agents, and access to adherence support, is essential to limit the development of resistance and loss of these effective new regimens.

M.O. is supported by National Institutes of Health/ National Institute of Allergy and Infectious Diseases (R01AI124413, R01AI167795) and by the National Center for Advancing Translational Sciences (UL1TR001873). This work was supported by grants from the Wellcome Trust to C.N. (203583/Z/16/Z) and J.M. (203919/Z/16/Z). C.N. is supported by the Francis Crick Institute, which receives its core funding from Cancer Research UK (CC2169), the UK Medical Research Council (CC2169), and the Wellcome Trust (CC2169).

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## References

1. World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: The Organization; 2022 [cited 2022 Oct 6]. <https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2>
2. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al.; ZeNix Trial Team. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med*. 2022;387:810–23. <https://doi.org/10.1056/NEJMoa2119430>
3. Nyang'wa B-T, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al.; TB-PRACTECAL Study Collaborators. A 24-week, all oral regimen for rifampicin-resistant tuberculosis. *N Engl J Med*. 2022;387:2331–43. <https://doi.org/10.1056/NEJMoa2117166>
4. Nimmo C, Millard J, van Dorp L, Brien K, Moodley S, Wolf A, et al. Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa: a phenotypic and phylogenetic analysis. *Lancet Microbe*. 2020;1:e165–74. [https://doi.org/10.1016/S2666-5247\(20\)30031-8](https://doi.org/10.1016/S2666-5247(20)30031-8)
5. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med*. 2015;373:1986–8. <https://doi.org/10.1056/NEJMc1505196>
6. Polsfuss S, Hofmann-Thiel S, Merker M, Krieger D, Niemann S, Rüßmann H, et al. Emergence of low-level delamanid and bedaquiline resistance during extremely drug-resistant tuberculosis treatment. *Clin Infect Dis*. 2019;69:1229–31. <https://doi.org/10.1093/cid/ciz074>
7. Yoshiyama T, Takaki A, Aono A, Mitarai S, Okumura M, Ohta K, et al. Multidrug resistant tuberculosis with simultaneously acquired drug resistance to bedaquiline and delamanid. *Clin Infect Dis*. 2021;73:2329–31. <https://doi.org/10.1093/cid/ciaa1064>
8. Omar SV, Ismail F, Ndjeka N, Kaniga K, Ismail NA. Bedaquiline-resistant tuberculosis associated with *Rv0678*

- mutations. *N Engl J Med.* 2022;386:93–4. <https://doi.org/10.1056/NEJMc2103049>
9. O'Donnell MR, Padayatchi N, Wolf A, Zelnick J, Daftary A, Orrell C, et al. Bedaquiline adherence measured by electronic dose monitoring predicts clinical outcomes in the treatment of patients with multidrug-resistant tuberculosis and HIV/AIDS. *J Acquir Immune Defic Syndr.* 2022;90:325–32. <https://doi.org/10.1097/QAI.0000000000002940>

10. Fowler P; CRYPTIC Consortium. Epidemiological cut-off values for a 96-well broth microdilution plate for high-throughput research antibiotic susceptibility testing of *M. tuberculosis*. *Eur Respir J.* 2022;60:2200239. <https://doi.org/10.1183/13993003.00239-2022>

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## COMMENT LETTER

### Nomenclature for Human Infections Caused by Relapsing Fever *Borrelia*

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DOI: <https://doi.org/10.3201/eid2905.230195>

**To the Editor:** Vazquez et al. report a convincing case of relapsing fever caused by *Borrelia lonestari* bacteria (1). This discovery highlights an existing problem with the nomenclature for relapsing fever.

Tick-borne relapsing fever (TBRF) is the name given to illness caused by several genospecies of relapsing fever *Borrelia* bacteria, all of which are transmitted by argasid (soft) ticks (2). The limitations of this term became apparent after discovery of *B. miyamotoi*, a related genospecies that is transmitted by ixodid (hard) ticks and causes illness that differs epidemiologically from traditional TBRF (3). Consequently, 3 terms are used in the scientific literature to describe *B. miyamotoi* infections: *Borrelia miyamotoi* disease, hard tick-borne relapsing fever, and hard tick relapsing fever (3,4). In the interest of standard nomenclature, it is worth considering objectively the relative merits of each term.

The term *Borrelia miyamotoi* disease (BMD) is problematic because it is species specific and cannot accommodate the discovery of related pathogens transmitted by ixodid ticks, including potentially *B. lonestari* (1,3). Disease names are most serviceable as

umbrella terms that exist above the species level (e.g., Lyme disease, shigellosis).

The term hard tick-borne relapsing fever has a different problem, a grammatical one. The word hard rightly modifies tick, not tick-borne, which is a mode of transmission. This problem is solved by shortening to hard tick relapsing fever. The suffix “-borne” is not essential for clarity, as demonstrated by other established names (e.g., sand fly fever, Colorado tick fever) (2).

In the absence of a formal nomenclature decision by the World Health Organization, the following terms are consistent with precedent, epidemiologically useful, linguistically sensible replacements for TBRF: hard tick relapsing fever (HTRF) for illness caused by relapsing fever-clade *Borrelia* transmitted by ixodid ticks, and its congener, soft tick relapsing fever (STRF), for related agents transmitted by argasid ticks.

#### References

- Vazquez Guillemet LJ, Marx GE, Benjamin W, Pappas P, Lieberman N, Bachiashvili K, et al. Relapsing fever caused by *Borrelia lonestari* after tick bite in Alabama, USA. *Emerg Infect Dis.* 2023;29:441–4. <https://doi.org/10.3201/eid2902.221281>
- World Health Organization. International Classification of Diseases, 11th revision. 2022 [cited Jan 31]. <https://icd.who.int>
- Telford SR III, Molloy PJ, Berardi VP. *Borrelia miyamotoi*. *Ann Intern Med.* 2015;163:963–4. <https://doi.org/10.7326/L15-5187>
- Rodino KG, Pritt BS. When to think about other *Borrelia*: hard tick relapsing fever (*Borrelia miyamotoi*), *Borrelia mayonii*, and beyond. *Infect Dis Clin North Am.* 2022;36:689–701. <https://doi.org/10.1016/j.idc.2022.04.002>

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## Correction

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The Figure had an incorrect x-axis scale in Laboratory Features of Trichinellosis and Eosinophilia Threshold for Testing, Nunavik, Quebec, Canada, 2009–2019 (L.B. Harrison et al.). The article has been corrected online ([https://wwwnc.cdc.gov/eid/article/28/12/22-1144\\_article](https://wwwnc.cdc.gov/eid/article/28/12/22-1144_article)).

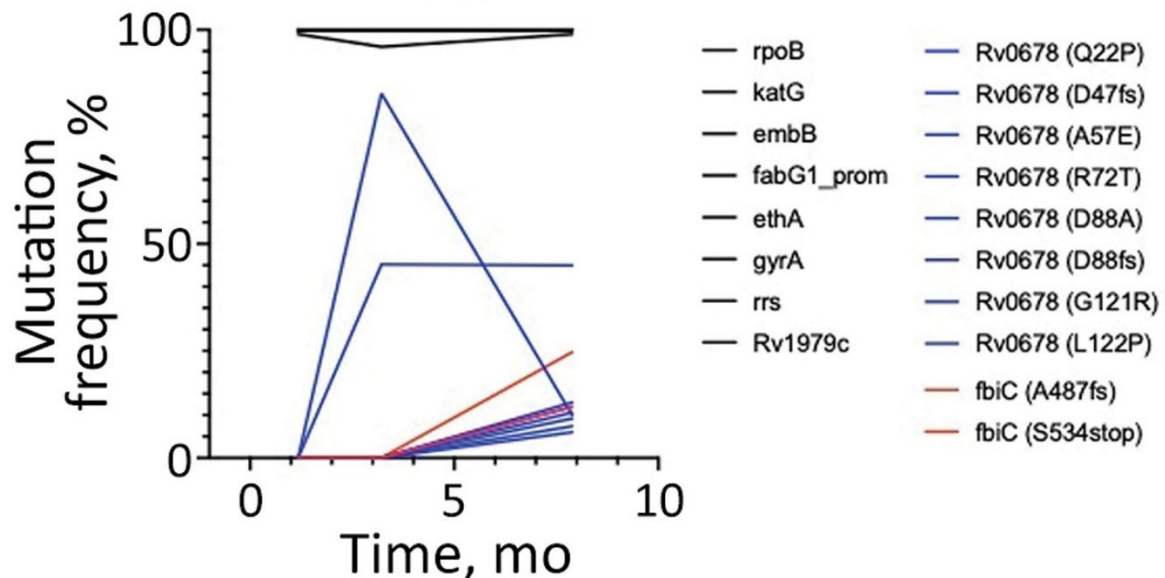


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# Therapeutic Failure and Acquired Bedaquiline and Delamanid Resistance in Treatment of Drug-Resistant TB

## Appendix



**Appendix Figure.** Whole-genome sequencing mutations and their frequencies over time color matched to corresponding development of drug resistance over time. Red indicates delamanid resistance, blue indicates bedaquiline resistance.